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ORIGINAL

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant	:	José Calatayud et al.
Serial No.	:	578,942
Filed	:	September 7, 1990
Title	:	NEW PREGNA-1, 4-DIENE-3, 20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS
Group Art Unit	:	1202
Examiner	:	M. Grumbling
Attorney Docket	:	RCS 2 001

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Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

BRIEF ON APPEAL

Applicant has properly appealed to the Board of Patent Appeals and Interferences as detailed in 37 C.F.R. § 1.191 this Brief is submitted in accordance with 37 C.F.R. § 1.192 within six (6) months of the date of the Notice of Appeal including an extension of one additional month for which an extension request under 37 C.F.R. 1.17 and a check in the amount of $270.00 is enclosed herewith. This Brief is submitted in triplicate and in the format now required under 37. C.F.R. § 1.192.

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STATUS OF CLAIMS

Claims 1-3 and 17-20 remain in the application. Claims 1-3 and 17-20 have been finally rejected by the Examiner. Claims 4-12 have been withdrawn from consideration. Claims 14 and 15 have been canceled.

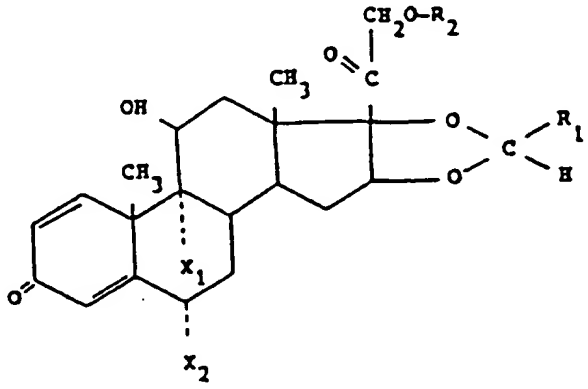
STATUS OF AMENDMENTS

An Amendment After Final Rejection was filed on January 19, 1993, seeking to amend claims 18 and 20. The Examiner sent an Advisory Action on February 10, 1993, indicating that the rejections under 35 U.S.C. §101 and 35 U.S.C. §112 have been overcome, but that the rejections under 35 U.S.C. 103 have not yet been overcome because Applicants' data was not in declaration form. This is being addressed by Applicants at this time.

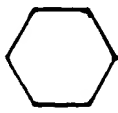
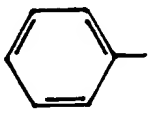
SUMMARY OF INVENTION

The composition of the present invention provide certain glucocorticoids which have a combination of high anti-inflammatory activity at the application site and a low systemic glucocorticoid activity.

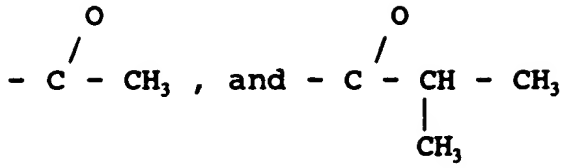
The compounds according to the invention are characterized by the formula:



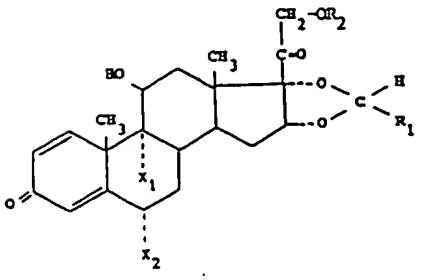
in which X_1 and X_2 correspond to H or F without distinction; R_1 represents the following radicals:

$CH_2-CH_2-CH_2-CH_3$, $CH(CH_3)-CH_3$, $-CH(CH_3)-CH_2-CH_3$,  , and 

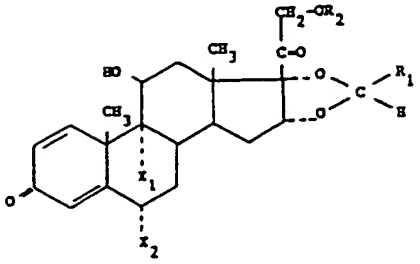
R_2 represents the radicals



Each of these compounds has 2 stereoisomer components (epimers), which in relation to the general formula (I), may be represented in the following manner:



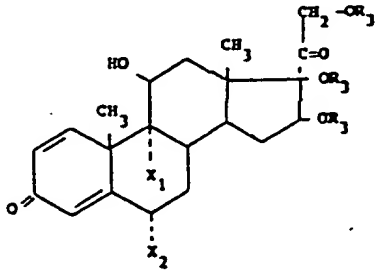
(II)
(S epimer)



(III)
(R epimer)

In the diastereoisomers (II) and (III), the different configuration corresponds to C-22 (asymmetric carbon). These diastereoisomers take the name S and R epimers.

The compounds of this invention are prepared by hydrolysis-ketalization --with a suitable adequate catalyst which will be indicated in the corresponding cases-- from the compounds triesterified at C-16, C-17, and C-21, whose structure is indicated below:



in which R_3 corresponds to an acetyl or isobutyl radical and X_1 and X_2 represent H or F without distinction.

ISSUES

1. Can the Examiner's rejection of Applicants' claims be sustained when the references as fairly taken do not teach the compositions of Applicants' invention or materials which can satisfy parameters for which the compositions of Applicants' invention were created.

2. Can the Examiner's rejection of Applicants' novel composition claims be sustained when that rejection is based upon a piece-meal reconstruction of the prior art in which the Examiner takes individual, specific teachings from a combination of references while ignoring all of the remaining teachings of those references which are either unsuitable and/or contrary to Applicants' teachings, and where there is no teaching in any of the references which would lead one skilled in the art to combine the teachings in the manner which the Examiner now makes in an effort to meet the limitations of Applicants' claims.

In the argument which follows, various articles are cited by references to the articles enclosed with Applicants' Amendment After Appeal which are identified by corresponding numbers.

ISSUE 1

1. The Examiner's rejection of claims 1, and 17-20 under 35 U.S.C. §103 as being unpatentable over Brattsand et al. (U.S. Patent No. 3,983,233) have been respectfully traversed.

The Examiner indicates the data provided are not sufficient to overcome the rejection because:

(a) The data are not presented in declaration form. A proper declaration is being submitted.

(b) It is not possible to determine from the data whether they were acquired under the same conditions because Meier is a foreign language reference which the Examiner cannot comprehend. A copy has been made available with Applicants' Amendment After Appeal.

(c) The results presented are not convincing because the Therapeutic Index values for Example 16 of Brattsand et al. and EL-854 are very similar and one of skill in the art would expect the two to have similar activities due to their similar structures.

Ted Tse (1) teaches about the groups essential to anti-inflammatory activity in the basic structure of glucocorticoids. If these groups are present, this pharmacological activity will be preserved. The structure for the claim compounds is in concordance with the basic structure of the glucocorticoids with anti-inflammatory activity (2). Because of this, from a general point of view, the products included in the instant patent application, and all of the compounds structurally related, as those included in the reference patents cited by the Examiner are, show qualitatively common responses.

Structural modifications which preserve the basic structure, as well as the above-mentioned essential groups for anti-inflammatory activity, should be related to quantitative modifications of the same pharmacological responses. So, the goal in the development of new corticoids with anti-inflammatory activity of therapeutic utility, will be <u>to obtain a better quantitative response</u>.

Szefler (2) suggests:

> "Although it is feasible to develop synthetic agents that have more potent glucocorticoid effect as compared to mineralocorticoid effects, it is not possible to separate the anti-inflammatory effects of glucocorticoids from the metabolic effects. Furthermore, the glucocorticoids significantly suppresshypothalamic-pituitary-adrenocortical (HPA) function".

He also states:

> "It must be recognized that methods to increase the anti-inflammatory effects are associated with an increased risk for undesired effects, such as growth suppression, alterations in body habitus, osteoporosis,

> hypertension, and cataracts. Nevertheless, these agents are beneficial in managing many inflammatory disorders, such as asthma and collagen vascular disease, as well as neoplastic disease, shock, and inhibition of transplant rejection. Methods to optimize effect include the identification of compounds that maximize the ratio of glucocorticoid to mineralocorticoid effects, attempts to deliver the most drug to the relevant site of action, and to define dosing schemes to maintain beneficial effects while minimizing HPA axis suppression".

Clissold et al. (3) notes that:

> "A high ratio of local anti-inflammatory to systemic activity appears to be an important indicator relating therapeutic efficacy to systemic tolerability".

In line with this, research has been conducted on corticoids with a structure related to that of the compounds cited by Brattsand et al. (U.S. Patent Nos. 3,983,233 and 3,992,534) which result in a relative improvement in the therapeutic treatment of anti-inflammatory diseases. Among other authors are Brattsand himself (11) and McDonald (10).

From a quantitative point of view, both the general pharmacological activity as well as the ratio between local and systemic effects, are related essentially to the nature of the substituent radicals and the metabolic pattern of the compounds (11, 12). Relevant differences can be found between compounds containing structurally similar radicals and a structure-activity relationship for the substituent is not known up to today. From the foregoing, it is clear that a higher intrinsic local anti-inflammatory activity and a lower systemic glucocorticoid effect

are the desirable properties for a new glucocorticoid intended for topical action, that these properties are related to the nature of the substituent groups and that is not predictable in this relation.

However, the Examiner alleges (Paper No. 6, page 6, second paragraph) that:

> "The claimed compounds, compositions and methods of use would have obvious to one of ordinary skill in the art at the time the invention was made because the claimed compounds are structurally related compounds which would be expected to have similar chemical and pharmaceutical properties."

In the patent of Brattsand (A) mentioned by the Examiner, compounds referred in Examples 1, 2, and 3 correspond to the following structures:

Example 1: (Column 3, line 57)

16α,17α-(2'-hydrogen-2'-**ethyl**) methylene dioxy-9-fluoropregna-1,4-diene-11ß,21-diol-3,20-dione

Example 2: (Column 9, Table in line 46)

16α,17α-(2;-hydrogen-2α-**n-propyl**)methylenedioxy-9-fluoropregna-1,4-diene-11ß,21-diol-3,20-dione

Example 3: (Column 9, Table in line 46)

16α,17α-(2'-hydrogen-2'-**n-butyl**)methylene dioxy-9-fluoropregna-1,4-diene-11ß,21-diol-3,20-dione

So, these three compounds conform a homolog series in respect to radical R_1 of the general formula.

The biological effects of these compounds are summarized by Brattsand in Table 5 of his patent (column 9) and they are

reproduced in the following table (a column indicating therapeutics index values, obtained as the quotient between the ED_{50} values for systemic and topical activities, is included).

Compound	R1	Topical Anti-inflammatory activity (Cotton Pellet)	Systemic glucocorticoid activity (Thymus inhib)	Therapeutic Index Systemic ED50/ Topical ED50
Ex. 1	Ethyl	35	100	2.86
Ex. 2	n-Propyl	10	> 30	> 3
Ex. 3	n-Butyl	< 3	70	> 23

From the data contained in this table, it can be seen that, in relation to the three compounds of the mentioned homolog series:

(a) The ED_{50} values for topical activity are in the range <3 and 35 μg, that is, they differ by a factor of at least 10.

(b) The ED_{50} values for systemic activity are in the range >30 and 100 μg, that is, they differ by a factor of 3.

(c) The values for therapeutic index are in the range 2.86 and 23 μg, that is, they differ by a factor of at least 8.

So, from the data contained in the patent of Brattsand, it is clear that what would have been obvious to one of ordinary skill in the art at the time the invention was made was that structurally related compounds would NOT be expected to have similar pharmaceutical properties.

This conclusion is of application to the compounds included in the instant patent application, as well as those claimed by Brattsand in the mentioned patent.

The Examiner specifically has mentioned compound 16 presented in Table 4, column 5, of Brattsand (A), indicating the structural similarity with the compound claimed in the instant application in which R_1 is butyl and R_2 is acetyl. The present patent application does not cover experimental data on the pharmacological activity of said compound; however, the data are available in proprietary files (compound EL-854). The comparison of these data with compound 16 of Brattsand is indicated below:

Compound	Topical anti-inflammatory activity (Cotton Pellet)	Systemic glucocorticoid activity (Thymus inhib)	Therapeutic Index Systemic ED50/ Topical ED50
Ex. 16 U.S. Patent No. 3,983,233	< 3	30	> 10
EL-854	8.6	147	17.1

From the data contained in this table, it is derived that:

(a) The ED_{50} values for topical activity differ by a factor of at least 3.

(b) The ED_{50} values for systemic activity differ by a factor of 5.

Applicants are preparing to present the foregoing data in declaration form as soon as possible; but, since the Applicants reside in Spain and because of the language difficulties, filing of the declaration has been developed.

The Applicants consider that these results do not support the assessment of the pharmacological activities of both compounds are similar, especially if the scope of minimize systemic glucocorticoid effect on claim 18 is taken in consideration.

Neither the compound indicated by the Examiner (the above-mentioned EL-854) nor any other of the compounds claimed in the instant application are specifically mentioned in the patent of Brattsand et al.

Moreover, the compounds claimed in this application show pharmacological properties of patentable utility because there are differences not obvious at the time the invention was made to a person having ordinary skill in the art between the subject matter sought to be patented and the prior art.

This assessment is derived from comparison of the values of anti-inflammatory potency of the compounds from the instant invention and the corresponding values of those included in the patent of McDonald (U.S. Patent No. 4,835,145) Tables II and III (10). The results on relative potency of the compounds included in the instant invention are derived form the quotient ED_{50} (22 R,S)-compound (column "topical anti-inflammatory activity" on table III from the instant invention).

The results are shown in the following table:

Patent	Compound	Relative Topical anti-inflammatory potency (Budesonide = 1)
U.S. Patent No. 3,983,233 (Brattsand)	Ex. 22 (More potent of all the compounds)	1.49*
U.S. Patent No. 4,835,145 (McDonald)	2 e 2 f 2 g 2 i	3.03 4.86 1.80 5.90
U.S. Patent Application Serial No. 578,942 (Calatayud)	7 10 13	7.54 2.73 36.35

*=Table III of U.S. Patent No. 4,835,145

The pharmacological data of the compounds of the instant invention are compared with those included in the patent of McDonald because:

(a) The patent of McDonald is later than that of Brattsand and represents the latest teaching of the relevant art.

(b) Data on pharmacological activity mentioned by McDonald were acquired by the same test method employed by the instant Applicants [Method of Meier et al. (8)].

(c) Budesonide is used as reference compound by McDonald and the Applicants. In this way, possible differences in experimental conditions are overcome.

From this data is derived that the compounds claimed in the present patent application show a better anti-inflammatory potency that those included in the patents of reference.

This better response can be related to:

(a) Bulkiness of the substituents, because bulk differences in R_1 can provide better responses (12).

(b) A better topical anti-inflammatory response.

Moreover, it is clear from the data presented in Table III of the specification that the compounds included in this application possess a better relation between the topical anti-inflammatory activity and systemic effects. This can be due to metabolic patterns of the compounds of the instant invention. Comparative studies on inactivation of Ciclesonide* by hepatic oxigenases show that the systemic action of Ciclesonide is lower than that action of Budesonide by p.o. and s.c. routes of administration. (13)

From the foregoing discussion, it is clear that:

(a) Though they are structurally related, the compounds claimed in the instant patent application are not specifically disclosed or suggested by the references.

(b) They show higher topical anti-inflammatory activity (inhibition of the growth of the granuloma) and lower systemic effects (reduction of the thymus weight), and more advantageous hepatic metabolism; and, therefore, a better therapeutic index than the steroids of the prior art.

As a result, the use of the compounds claimed in the present application are not a matter of preference depending on factors not related to pharmaceutical properties, but represents an unexpected therapeutic improvement with regard to other steroids; and, therefore, could be considered patentable.

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*Ciclesonide: Name given to the Compound No. 7 by the INN of the WHO.

ISSUE 2

The Examiner's rejection of claims 1-3, and 17-20 under 35 U.S.C. §103 as being unpatentable over Brattsand et al. (U.S. Patent No. 3,983,233) as applied above in view of Brattsand et al. (U.S. Patent No. 3,992,534) was also traversed.

In response to the last paragraph of page 6 to page 7 of the Office Action (Paper No. 6) regarding epimers claimed in the present invention, and their structural similarity to the Brattsand et al. compounds (A) and (B), Applicants note:

(a) Applicants feel that the differences indicated above between the compounds of claim 1 of the instant application and the reference patents cited by the Examiner are also valid in the case of the isolated epimers of these compounds.

(b) The products included in the instant patent application, as well as those mentioned by Brattsand et al., contain a chiral center in C-22 and, consequently, they can exist as mixtures of epimers. Nevertheless, none of the epimers claimed in the present application are specifically included in or suggested by Brattsand et al. (U.S. Patent No. 3,992,534).

(c) Brattsand et al. (U.S. Patent No. 3,992,534) specifically mentions the compounds of their Examples 1, 3, 5, 7, 8, and 12 as preferred, based upon the characteristics of component B.

The pharmacological data of these compounds and their epimers preferred by Brattsand Table 3, columns 10 and 11, are compared with the data corresponding to instant compounds (Table III of our patent application).

Compound		µg/animal to obtain 50% inhibition of		Therapeutic Index ED50 Thymus/ ED50 Granuloma
		Granuloma growth	Thymus weight	
Ex. 1*	A + B	120	270	2.25
	A	270	115	0.42
	B	30	50	1.66
Ex. 3*	A + B	10	> 30	3
	A	25	> 30	1.2
	B	3	17	5.6
Ex. 7*	A + B	no data	no data	-
	A	15	12	0.8
	B	10	6	0.6
Ex. 8*	A + B	5	10	2
	A	6	13	2.1
	B	4	10	2.5
Ex. 12*	A + B	100	80	0.8
	A	125	125	1
	B	40	70	1.75
Ex. 7** 22 R,S		21.7	614.7	28.3
Ex. 8** 22 S		20.5	608	29.6
Ex. 9** 22 R		25.4	667.1	26.2
Ex. 10** 22 R,S		59.9	583.2	9.7
Ex. 11** 22 S		43	555.3	12.9
Ex. 12** 22 R		74.7	592.2	7.9
Ex. 13** 22 R,S		4.5	54	12
Ex. 14** 22 S		3.6	49	13.6
Ex. 15** 22 R		5.2	56.3	10.8

*=Brattsand (B) (U.S. Patent No. 3,992,534
**=U.S. Patent Application No. 578,942

From these data, it is clear that in all the cases, the therapeutic index of the compounds claimed in the instant application and their epimers are more favorable than those shown by the compounds

mentioned by Brattsand et al. and component B of the aforementioned Brattsand compounds.

From the foregoing discussion, we can consider that:

(a) Though they are broadly and structurally related, the epimers claimed in the present application are neither specifically mentioned nor in any way suggested by or obvious from the teaching of the cited references.

(b) They show an unexpected, better relationship between local anti-inflammatory activity and systemic effects than the epimers claimed in the reference patent. So a better therapeutic index than that of the steroids of the prior art is clear. This means a significant therapeutic improvement in relation with other glucocorticoids.

On the other hand, the corticosteroid of the instant invention are physiologically active compounds, possessing anti-inflammatory activity according with the data included in the specification (Table III); but, this activity is higher than well-known reference compounds: Budesonide, Triamcinolone Acetonide, and Flunisolide.

Table III (Included in the declaration form)

Local pharmacologic activity and systemic glucocorticoid effects expressed as ED50 µg/pellet

Compound	Epimer	Topical Anti-inflammatory Activity (Cotton Pellet)	Systemic Glucocorticoid Activity (Thymus Inhib)	Therapeutic Index Systemic ED50/ Topical ED50	Therapeutic Index with Respect to Budesonide
7	22 R,S	21.7 (17 - 27.7)	614.7 (279.6 - 1351)	28.3	26
8	22 S	20.5 (16.9 - 25.6)	608 (359.3 - 1228.3)	29.6	27.2
9	22 R	25.4 (18.2 - 31.1)	667.1 (321.4 - 1489.2)	26.2	24.5
10	22 R,S	59.9 (59.3 - 60.3)	583.2 (236.2 - 1440)	9.7	8.9
11	22 S	43 (38.4 - 58)	553.3 (296.3 - 1387.3)	12.9	11.5
12	22 R	74.7 (65.1 - 83.3)	592.2 (265.1 - 1342.9)	7.9	7.2
13	22 R,S	4.5 (3.7 - 5.5)	54 (33 - 83.3)	12	11
14	22 S	3.6 (3 - 4.5)	49 (30.7 - 76.2)	13.6	15
15	22 R	5.2 (3.6 - 6)	56.3 (29.8 - 88.3)	10.8	9.9
Budesonide	22 R,S	163.6 (125.1 - 213.9)	178.6 (81.3 - 392.6)	1.09	1
Triamcinolone		220.7 (198.1 - 245.7)	156.4 (144.7 - 169)	0.7	0.6
Flunisolide		351.6 (268.8 - 459.9)	156 (133.3 - 224.8)	0.44	0.4

The experimental procedure used has been described by Meier et al. (8)**, and this test has been used by many authors to evaluate the anti-inflammatory activity of new compounds. Freeman et al. (9), pp. 573, line 14, states: "The original test of Meier appears

** We annex hereto a copy of the original publication in German and English translation.

to have the advantage that it provides a method of distinguishing steroidal type drugs from their non-steroidal counterparts". Also, McDonald (10) acknowledges: "The U.S. Patent No. 4,835,145 example described the use of the Meier test to evaluate the anti-inflammatory activity of different new corticoids." We can thus conclude that to one of ordinary skill in the art, the cotton pellets induced granuloma used by Meier et al., could be considered valid to study the local anti-inflammatory activity and also systemics effects in the form of retrogression of thymus and inhibition of body weight.

The anti-inflammatory potencies found in the screening models as that used by Meier et al., intended for evaluation of the topical anti-inflammatory activity thus seem to also be a rather good prediction of the anti-asthmatic activity in humans.

In this way, we also rely on U.S. Patent No. 4,835,145, in which there are several claims (claim nos. 3, 6, 9, 12, and 15) related to a method of treating inflammatory conditions, on the basis to a topical anti-inflammatory efficacy derived from the ability to inhibit cotton pellet induced granuloma by the method described by Meier et al.

Since the compounds of the instant invention are corticoids, the utility of these drugs is based on its anti-inflammatory activity, which anti-inflammatory activity has been demonstrated in the specification using a valid method for this purpose, we conclude that one of ordinary skill in the art would accept the

utility of the compounds described in the invention as obviously valid for the use in humans.

CONCLUSION

For the foregoing reasons and in keeping with established law and rules, Applicant respectfully submits that the claims presently in the application distinctly claim patentable subject matter, that Applicants' novel composition clearly exhibits highly unexpected and very desirable properties, and that the Examiner should be reversed. Reversal of the Examiner, allowance of the claims, and passage of the case to issue is respectfully solicited.

Respectfully submitted,

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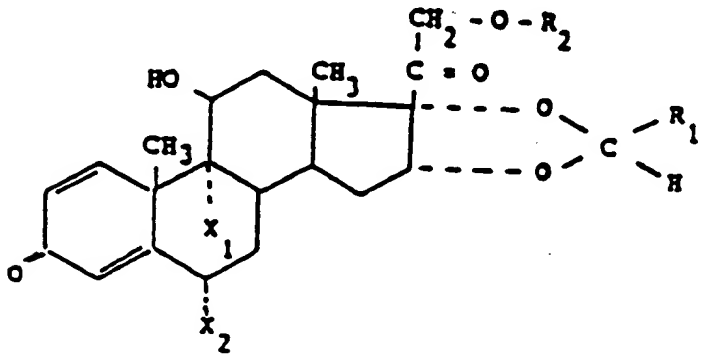
CERTIFICATE OF MAILING

I hereby certify that this Brief On Appeal is being deposited with the United States Postal Service as Express Mail No. TB244106401 addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231, on February 19, 1993.

Sally A. Major

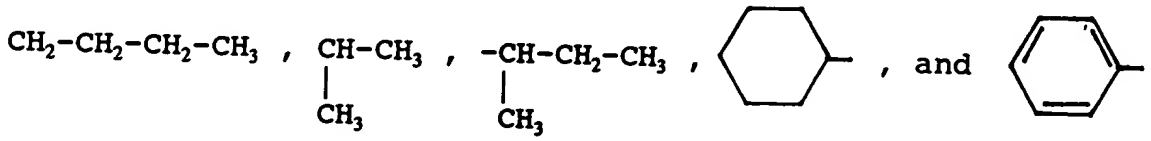
CLAIMS PENDING
IN U.S. PATENT APPLICATION NO. 578,942

1. A compound of the formula



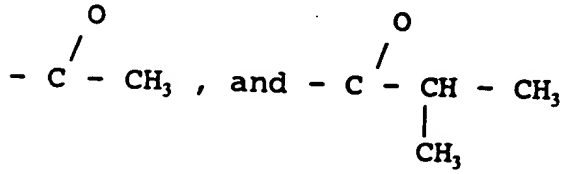
in the form of an R epimer, an S epimer, or a stereoisomeric mixture of the R and S epimers in terms of the orientation of the substituents on the carbon atom at position 22, wherein:

R_1 is a member selected form the group consisting of



and

R_2 is a member selected from the group consisting of



and wherein X_1 and X_2 may be the same or different and each is a member selected from the group consisting of hydrogen and fluorine.

2. A compound according to claim 1 in the form of the (22S)-epimer.

3. A compound according to claim 1 in the form of the (22R)-epimer.

17. An anti-inflammatory drug containing a compound according to claim 1.

18. A method of treating inflammatory conditions which comprises administering to a patient an anti-inflammatory effective amount of a compound according to claim 1.

19. A pharmaceutical composition having anti-inflammatory properties comprising as the active ingredient an effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.

20. A method for the treatment and control of inflammatory conditions characterized by the topical administration to a patient of an effective dose of a compound according to claim 1.